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The devil's advocate editorial on screening HLA to prevent severe drug reactions

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Severe cutaneous adverse [drug] reactions (SCAR) are delayed-onset drug hypersensitivity reactions that carry significant morbidity and mortality and impose a major economic burden on healthcare systems.[1,2] 2002 heralded a breakthrough in SCAR and pharmacogenomics research with the discovery that HLAB*57:01 strongly associated with abacavir-induced Drug-Induced Hypersensitivity Syndrome/Drug Rash with Eosinophilia and Systemic Symptoms (DIHS/DRESS, a type of SCAR).[3] Mallal et al, then published in 2008 beautiful evidence that supported screening HIV patients for HLA-B*57:01 prior to initiating abacavir treatment to prevent DIHS/DRESS.[4] The field has since exploded, with dozens of HLA-drug associations identified in the context of specific drug reactions.[5,6] Resultingly, an increasing number of studies aimed at evaluating the utility of screening HLA to prevent SCAR are being performed. A recent systematic review highlighted the association between dapsone-induced SCAR and HLA-B*13:01.[7] In this issue of *JAMA Dermatology*, Liu et al, demonstrated that screening for HLA-B*13:01 prior to initiating dapsone therapy in leprosy patients in China prevented DIHS/DRESS, thus supporting a role for HLA screening.[8]

Is the decision to screen HLA so simple though? This era of personalized medicine has witnessed advancements in technologies capable of detailing an individual's genetics in less time and at lower cost. After all, for just $139 (holiday sale) 23andMe will test your DNA to determine your "Health" and "Ancestry"! Moreover, if we can prevent an individual from developing a potentially devastating case of SJS/TEN or DIHS/DRESS, are we not obligated to do so?

The current state of research in this field is not without challenges, limiting data interpretation and generalizability. Several factors ranging from technical constraints in HLA typing to the epidemiology of ethnicity and disease to healthcare costs are at play.

First, rigorous data supporting the association between one (to a few) specific HLA alleles and a culprit drug in the context of a defined drug reaction are necessary. One major obstacle in drug reaction research is reporting bias due to (i) the absence of defined clinical phenotypes and (ii) uncertainty in identifying the culprit drug. The former is particularly true of studies of DIHS/DRESS which lack agreed upon diagnostic criteria and of SJS which may be confused clinically with mycoplasma mucositis, erythema multiforme, or bullous

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fixed drug. Mallal et al's study demonstrating the utility of HLAB*57:01 screening to prevent abacavir-induced DIHS benefited from diagnosis-confirming patch testing of abacavir.[4] Unfortunately, few drugs are testable by patch or other *ex vivo* assay, therefore necessitating reliance on clinical opinion alone. Second, many studies are either entirely retrospective or compare the prospective HLA screened arm to historical controls. This is partly secondary to ethical constraints, as administering an at-risk drug to someone possessing the predisposing HLA is potentially dangerous.

Moreover, genetic screening requires a laboratory method that is cost effective, reliable (high sensitivity, specificity and predictive values), and practical. Multiple laboratory techniques are currently used for HLA typing both clinically and in research. Methods vary widely in cost, technical difficulty/efficiency, result ambiguity, and sensitivity and specificity.[5,9] The advent of Next Generation Sequencing has revolutionized the field by improving accuracy and resolving ambiguity,[10] but it is expensive. The screening method employed can therefore impact both pharmacogenomic and cost-effectiveness analyses.

Further complicating matters, not all patients who screen positive for a predisposing HLA allele develop a drug reaction despite receiving the at-risk drug, i.e. positive predictive value (PPV) of HLA screening is highly variable.[11] For example, while HLA-B*57:01 is estimated to have a 55% PPV for abacavir-induced DIHS/DRESS, HLA-B*15:02 is estimated at only 3% PPV for carbamazepine-induced SJS/TEN.[11] Technical limitations contribute to this variability, but there are probably additional, less obvious factors. Is it a concurrent viral infection overturning peripheral tolerance mechanisms, or is the patient a slow metabolizer or have compromised excretion resulting in high drug levels? The existence of protective HLA alleles against specific drug reactions has also been suggested.[12] These are active areas of research with early supportive evidence but are likely only the tip of the iceberg. Regardless of underlying reason, if HLA screening has low positive predictive value, screening may not be warranted. An interesting nuance is whether the benefit of screening HLA for specific drug/drug reaction is dependent on underlying disease. Liu et al, contemplated in their article whether their findings of screening to prevent dapsone-induced DIHS in leprosy patients is applicable to patients with underlying inflammatory conditions responsive to dapsone.[8] Given the existence of additional "X" factor(s) in determining patient susceptibility to drug reactions, it may be premature to assume generalizable.

Additionally, if the prevalence of a specific HLA allele is low amongst a population, the cost of screening will grow relative to its benefit. This runs concurrent to a population's heterogeneity. While screening for HLA-B*15:02 is clearly beneficial in Taiwan, where ~8% population is HLA-B*15:02 positive,[13] blindly screening the United States' population for the same HLA allele before starting carbamazepine would be outrageously expensive with little yield. To this point, the US Food and Drug administration recommends HLA-B*15:02 screening prior to initiating carbamazepine treatment in persons of Asian ancestry.[14] A study in Malaysia similarly concluded that broadly screening patients for HLA-B*15:02 in their ethnically-diverse population is not cost-effective.[15]

The consequences of having the drug reaction must be weighed against the consequences of drug avoidance. Most dermatologists are well aware of the potential devastation from SCAR. The consequences of drug avoidance may be overlooked. Do efficacious and safe alternative therapies exist? Are they affordable? Of course, in the absence of reasonable alternative agents, screening could still prove beneficial by alerting the clinician to closely monitor the patient or potentially initiate therapy at a lower dose. The *JAMA Dermatology* article by Liu et al, broaches a very intriguing potential consequence of excluding dapsone from treatment regimens in HLA-B*13:01 patients with leprosy: drug resistance. The study could not assess this owing to the slow growing nature of *Mycobacterium leprae* (drug resistance would not be appreciated for potentially several years).[8] What if the at-risk drug was used for treating tuberculosis? Or vancomycin-resistant enterococci?

The final challenge is defining and measuring the “benefit” or “utility” of screening. This is typically interpreted to mean cost-effectiveness, i.e. weighing cost of treating SCAR relative to cost of HLA screening and/or cost of alternative drugs. It may be exceedingly difficult to apply cost analyses performed in one society to another given stark differences in healthcare systems. Each society will likely need to perform independent cost-effectiveness analysis in the context of their healthcare system and in concert with the prevalence of predisposing HLA alleles and incidence of SCAR among HLA positive individuals in their respective population. Additional commonly used measures include lifetime saved, quality-adjusted life years gained and number needed to screen to prevent one case of drug reaction. These too are directly influenced by HLA and disease prevalence.

Conclusion:

Currently the FDA and other organizations such as the ACR recommend haplotype screening in select populations before starting specific drugs (i.e. abacavir, carbemazepine, allopurinol). As technology continues to advance and more HLA-drug associations are revealed, it may become cost-effective to preemptively HLA genotype each one of us to generate a personalized at-risk drug list. Until then, it seems prudent to rigorously collect, analyze and interpret the data in the context of specific populations, with the above caveats in mind, to determine the true value of HLA screening.

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